MULTIPLE MYELOMA: FROM THE BENCH TO BEDSIDE

Smoldering multiple myeloma

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Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell disorder. SMM is distinguished from monoclonal gammopathy of undetermined significance by a much higher risk of progression to multiple myeloma (MM). There have been major advances in the diagnosis, prognosis, and management of SMM in the last few years. These include a revised disease definition, identification of several new prognostic factors, a classification based on underlying cytogenetic changes, and new treatment options. Importantly, a subset of patients previously considered SMM is now reclassified as MM on the basis of biomarkers identifying patients with an ≥80% risk of progression within 2 years. SMM has assumed greater significance on the basis of recent trials showing that early therapy can be potentially beneficial to patients. As a result, there is a need to accurately diagnose and risk-stratify patients with SMM, including routine incorporation of modern imaging and laboratory techniques. In this review, we outline current concepts in diagnosis and risk stratification of SMM, and provide specific recommendations on the management of SMM. (*Blood*. 2015;125(20):3069-3075)

Introduction

Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell (PC) disorder.[1] Kyle and Greipp initially described the entity as an intermediate stage between monoclonal gammopathy of undermined significance (MGUS) and multiple myeloma (MM) on the basis of 6 patients with increased bone marrow PCs (≥10%) who remained stable for ≥5 years without chemotherapy.[2] SMM has since been well characterized, and high-risk subsets of SMM are increasingly recognized as the optimal phase of MM evolution in which to test early treatment strategies.[3-5]

SMM is distinguished from MGUS primarily for clinical reasons, because the risk of progression to malignancy in the first 5 years after diagnosis is different: 10% per year in SMM vs 1% per year in MGUS.[1] SMM is biologically heterogeneous; it is a clinically defined entity comprising a subset of patients with biological premalignancy (ie, MGUS) and a subset with biological malignancy (ie, MM) who have not yet developed hypercalcemia, renal failure, anemia, or lytic bone lesions (CRAB) and/or other myeloma-defining events (MDE).[6,7] Thus, SMM includes patients who behave like those with MGUS (with a very low rate of progression) and those who develop clinical symptoms and end-organ damage within the first 2 years of diagnosis.[3,4] It is unfortunate that at the current time, there is no single pathological or molecular feature that reliably can be used to distinguish SMM patients who have only clonal premalignant PCs from those who have clonal malignant myeloma cells.[6,8]

Definition

SMM is defined by the presence of a serum monoclonal (M) protein of ≥3 g/dL and/or 10% to 60% clonal bone marrow PCs (BMPCs) with no evidence of end-organ damage (ie, CRAB criteria) or other MDE.[7] It is distinguished from MGUS on the basis of the level of serum M protein and the percentage of clonal BMPCs (Table 1). The disease definition of SMM was recently updated to exclude patients with BMPCs of ≥60%, serum involved/uninvolved free light chain (FLC) ratio of ≥100, and those with 2 or more focal lesions (typically indicating focal bone marrow abnormalities) on magnetic resonance imaging (MRI).[7] Such patients have an approximately 40% per year risk of progression and are now considered to have MM.[9-14]

Light-chain SMM is a subtype of SMM in which there is monoclonal FLC excess with no expression of immunoglobulin heavy chain.[15] This entity is characterized by excess secretion of monoclonal FLC in the urine (Bence Jones proteinuria) (Table 1).

Clinical presentation and course

By definition, SMM is an asymptomatic condition. At this time, there is no population-based registry of SMM patients. According to available single-center registries, the typical age at SMM diagnosis is ~50 to 70 years. Because SMM is asymptomatic, newly diagnosed patients are typically diagnosed when an M protein is discovered on laboratory testing as part of the workup of a variety of disorders. Unlike MGUS, which is present in ~2% to 3% of the general population age >50 years,[16-18] SMM is a relatively uncommon clinical entity. A recent study based on the Swedish Myeloma Registry, a prospective observational registry designed to document real-world treatment and outcomes in newly diagnosed MM patients, 14% of the patients were classified as having SMM.[19]

The clinical course of SMM was reported by Kyle and colleagues in a retrospective study of 276 patients seen at the Mayo Clinic between 1970 and 1995.[1] In this study, the risk of progression to malignancy was

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Table 1. MGUS and SMM

Diagnosis	Disease definition	Progression rate	Reference
Non-IgM MGUS	Both criteria must be met: Serum M protein (IgG or IgA) <3 g/dL and clonal BMPCs <10%, and Absence of myeloma defining events or amyloidosis	1% per year	7
SMM*	Both criteria must be met: Serum M protein (IgG or IgA) ≥3 g/dL or urinary M protein ≥500 mg/24 h and/or clonal BMPCs 10%-60%, and Absence of MDEs or amyloidosis	10% per year in first 5 y. Light-chain SMM has a lower progression rate of 5% per year	7,15

*Excludes patients without end-organ damage who meet the revised definition of MM; namely, clonal BMPCs ≥60% or serum FLC ratio ≥100 (plus measurable involved FLC level ≥100 mg/L), or >1 focal lesion on MRI scan.

10% per year for the first 5 years. After 5 years, the risk of progression decreased to 3% per year for the next 5 years and ~1% per year thereafter. Thus, 50% of patients with newly diagnosed SMM progress within the first 5 years, and these patients probably have early MM without CRAB features. In contrast, approximately one-third of patients with newly diagnosed SMM will not progress in the first 10 years after diagnosis, and these patients probably have a premalignant state (biological MGUS), even though the clonal BMPC percentage or M protein level is higher than that specified in the clinical definition of MGUS.[3,6,20]

Risk factors for progression

The prognosis of SMM varies considerably, and it is possible to more accurately estimate risk of progression using a variety of prognostic variables. Although the variables listed in Table 2 and discussed in the following paragraphs were studied before the recent changes to the definition of SMM, the effect of such changes on the estimates is likely to be minimal because the proportion of patients upstaged from SMM to MM on the basis of the new criteria is relatively small (10%-15%).[7]

M protein concentration

In the previously mentioned retrospective study of 276 patients with SMM seen at the Mayo Clinic, Kyle and colleagues found that the size of the serum M protein was a significant risk factor for progression of SMM ($P < .001$).[1] The median time to progression (TTP) in patients with markedly elevated serum M protein levels (≥4 g/dL) was 18 months compared to 75 months in those with serum M protein levels <4 g/dL ($P < .001$). Similar results have also been reported by the Spanish Myeloma Group in a study of 93 patients with SMM.[21] In light-chain SMM, the risk of progression is higher depending on the level of the urinary M protein. In a study by Kyle and colleagues, the 5-year risk of progression of light-chain SMM was 19% in patients with 24-hour urinary M protein levels of 0.50 to 0.99 g per 24 hours vs 39% in those with urinary M protein levels of ≥1.0 g per 24 hours.[15]

M protein type

The type of M protein also influences the risk of progression in SMM. Kyle and colleagues found that TTP is significantly shorter in patients with immunoglobulin (Ig)A M protein compared to IgG M protein (median TTP, 27 vs 75 months, respectively; $P = .004$).[1] In a recent study, the risk of progression in patients with light-chain SMM was found to be lower, with a median TTP of 159 months; the probability of progression was 28%, 45%, and 56% at 5, 10, and 15 years, respectively.[15]

Immunoparesis

Suppression of ≥1 uninvolved immunoglobulins (immunoparesis) is seen in over 80% of patients; ~50% of patients have suppression of 2 uninvolved immunoglobulin isotypes.[1] In the Mayo Clinic study of 276 patients with SMM, immunoparesis was a significant risk factor for progression to MM or related disorder.[1] The median TTP was 159 months in patients with normal levels of uninvolved immunoglobulins, 89 months in those with a reduction in 1 isotype, and 32 months in patients with a reduction in 2 isotypes of uninvolved immunoglobulins ($P = .001$). The same effect was also seen in a Spanish study of SMM, in which a decrease in 1 or 2 of the uninvolved immunoglobulins was a significant prognostic parameter in SMM (median TTP, not reached with normal immunoglobulins vs 31 months with a reduction in ≥1 uninvolved immunoglobulins; $P < .01$).[21] Suppression of uninvolved immunoglobulins has also been found to be a risk factor for progression in light-chain SMM.[15]

Serum FLC ratio

The serum FLC assay (Freelite, The Binding Site Group, Birmingham, UK) measures free κ and λ light chains that circulate unbound to

Table 2. Definition of high-risk SMM

Clonal BMPCs ≥10% and any one or more of the following:
Serum M protein ≥30g/L
IgA SMM
Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes
Serum involved/uninvolved FLC ratio ≥8 (but <100)
Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period)
Clonal BMPCs 50%-60%
Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes
t(4;14) or del(17p) or 1q gain
Increased circulating PCs
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

The term SMM excludes patients without end-organ damage who meet the revised definition of MM; namely, clonal BMPCs ≥60% or serum FLC ratio ≥100 (plus measurable involved FLC level ≥100 mg/L), or >1 focal lesion on MRI scan. The risk factors listed are not meant to be indications for therapy; they are variables associated with a high risk of progression of SMM and identify patients who need close follow-up and consideration for clinical trials.

PET-CT, positron emission tomography with computed tomography.

immunoglobulin heavy chains.[22-24] The normal FLC κ:λ ratio is 0.26:1.65. In clonal PC disorders, there is excess production of one FLC type (the clonal component, referred to as the "involved" light chain), which often leads to an abnormal FLC ratio.[25] Dispenzieri and colleagues studied 273 SMM patients seen at the Mayo Clinic from 1970 to 1995.[26] An involved/uninvolved FLC ratio of ≥8 was a significant risk factor for progression (hazard ratio, 2.3; 95% confidence interval, 1.6-3.2; $P < .001$). Median TTP was 30 months in patients with an involved/uninvolved FLC ratio of ≥8 compared to 110 months for those with an FLC ratio <8. The risk of progression in the first 2 years after diagnosis is ~40% in patients with an involved/uninvolved FLC ratio of ≥8.

The risk of progression associated with an abnormal FLC ratio is a continuum.[26] Thus, when the involved/uninvolved FLC ratio rises to ≥100, the median TTP is only 15 months, and the 2-year risk of progression approaches 80%. Such patients are now considered to have MM.[10-12]

Change in M protein level

A key variable that could potentially identify patients with a high risk of progression is change in M protein levels over time. However, such studies have been hampered by the fact that patients with SMM have not been uniformly followed at specified intervals outside of clinical trials. In one study of 53 patients with SMM, patients with a progressive rise in M protein (evolving type) had a higher risk of progression compared with those with stable M protein levels.[27] In this study, the evolving type was defined as an increase in the serum M protein level by ≥10% on 2 successive evaluations. Patients with an evolving type of SMM had a 65% probability of progression to MM or related disorder in the first 2 years. TTP was 1.3 years in the evolving type vs 3.9 years in the nonevolving type of SMM ($P = .007$). A recent study by the Southwest Oncology Group found that patients with an M protein level of <3 g/dL that increased to ≥3 g/dL over 3 months was associated with a risk of progression of ~50% at 2 years.[28]

However, in the observation arm of the Spanish trial of SMM,[5] patients with a rise in M protein of ≥25% over 2 successive evaluations did not have a significant increase in risk of progression compared with patients without such a rise (2-year risk of progression, 69% vs 75%, respectively; M.-V.M., e-mail, March 28, 2014).

We believe that a rise in M protein level, especially over a short period of time, is of concern, and we await more data on how best to incorporate such a finding into the management of SMM.

Extent of bone marrow involvement

The risk of progression in SMM increases with the extent of bone marrow involvement. In the Mayo Clinic study, the median TTP was 117, 26, and 21 months for patients with BMPCs <20%, 20% to 50%, and >50%, respectively ($P < .001$).[1] Subsequent studies show that the risk of progression increases dramatically when the BMPC level is ≥60%, with a 2-year risk of progression of ~90%, and such patients are now considered to have MM.[9,10] BMPC estimate is done on the bone marrow aspirate or a core biopsy sample, or both, and in the event of a discrepancy, the higher of the 2 values should be used.[7]

Immunophenotype

Immunophenotyping with multiparametric flow cytometry is useful in determining prognosis in SMM by accurately distinguishing and quantitating BMPCs that have malignant potential from normal PCs.[5] Aberrant phenotype is defined by the absence of CD19 and/or CD45 expression, decreased expression of CD38, and overexpression of CD56. In MGUS, a substantial proportion of PCs are polyclonal and exhibit normal immunophenotype, whereas in MM, almost all PCs seen (>95%) are clonal and have an aberrant immunophenotype.[21,29,30] In a study of 93 patients with SMM, Pérez-Persona and colleagues found that 60% of patients with SMM have an aberrant immunophenotype similar to MM (>95% PC aberrancy; <5% of the detected PCs are normal).[21] The risk of progression in such patients was significantly higher as compared with those who had a lower rate of aberrancy in the detected BMPC population (median TTP, 34 months for patients with ≥95% aberrant PCs vs not reached for patients with <95% aberrant PCs; $P < .001$).

Table 3. Cytogenetically defined risk-based classification of SMM

Risk	Cytogenetic finding
High	t(4;14)
	del(17p)
	1q gain
Intermediate	Trisomies without IgH translocation
Standard	Other IgH translocations including t(11;14), t(14;16), and t(14;20)
	Presence of trisomies and IgH translocation, except t(4;14)
	Monosomy13/del(13q)
Low	No abnormalities (normal or insufficient)

IgH, immunoglobulin heavy chain.
Adapted from Rajkumar et al[31] with permission.

Tumor genetic abnormalities

Table 3 provides the classification of SMM based on underlying cytogenetic abnormalities.[31,32] The Mayo Clinic group recently analyzed the prognostic influence of cytogenetic abnormalities in a series of 351 patients with SMM.[31] Patients with t(4;14) and/or del(17p) were defined as high-risk SMM. These patients had a significantly shorter median TTP (24 months) compared with patients with trisomies (intermediate risk), other cytogenetic abnormalities including t(11;14) (standard risk), and no cytogenetic abnormalities (low risk). Similar results have also been reported by Neben and colleagues in a study of 249 patients with SMM.[32]

Dhodapkar and colleagues have assessed the value of gene expression profiling (GEP) signatures in 331 patients with MGUS and SMM.[28] An increased risk score (>−0.26) based on a 70-gene signature (GEP70) was an independent predictor of the risk of progression to MM. Further studies are needed to determine the incremental value of GEP compared to other, more readily available risk factors discussed earlier.

Circulating PCs

Bianchi and colleagues studied 91 patients with SMM who were tested for circulating PCs using an immunofluorescent assay.[33] A high level of circulating PCs was defined as absolute peripheral blood PCs $>5 \times 10^6$/L and/or >5% cytoplasmic immunoglobulin–positive PCs per 100 peripheral blood mononuclear cells. Patients with high circulating PCs were significantly more likely to progress to active disease within 2 years compared with patients without high circulating PCs (71% vs 25%, respectively; $P = .001$). However, the methods that have been published for estimating circulating PCs are not universally available, and cut points using multiparametric flow cytometric methods are needed.

Imaging

MRI is of prognostic value in SMM.[34] Moulopoulos and colleagues studied the prognostic value of spinal MRI in 38 patients with newly diagnosed asymptomatic MM.[35] Bone marrow abnormalities were detected in 50% of patients, including diffuse, variegated, and focal changes. Patients with MRI scans showing abnormal bone marrow changes had a median TTP of 16 months vs 43 months in those with normal MRI studies ($P < .01$). Further, median TTP was shorter in patients with focal lesions (6 months) as compared with those who had a diffuse (16 months) or variegated pattern (22 months). In a more recent study of 149 patients with SMM, Hillengass and colleagues detected focal lesions in 28% of patients using whole-body MRI, and the presence of such lesions was associated with an increased risk of progression to MM.[13] In the same study, the authors also confirmed the adverse prognostic effect of diffuse bone marrow changes detected by MRI (hazard ratio, 3.5; $P < .001$).

Of importance, in the study by Hillengass and colleagues,[13] 15% of patients had >1 focal lesion detected by whole-body MRI. The median TTP in such patients was 13 months, and the 2-year progression rate was 70%. Similar findings have been found in a study reported by Kastritis and colleagues[14] and in a study by Dhodapkar and colleagues.[28] Patients with >1 focal lesion are now defined as having MM and should not be considered as having SMM.[7]

Data are limited on the role of PET-CT in predicting risk of progression in SMM. However, patients who have focal lesions with increased uptake on PET-CT scans and who have underlying osteolytic destruction are not considered to have SMM; they are defined as having MM.[7] In contrast, we need data on the prognostic value of focal lesions that show increased uptake without underlying bone changes. The finding of an increased uptake on a PET-CT scan without bone destruction is not adequate to be considered an MDE.

PC proliferative rate

A high proliferative rate of clonal PCs is associated with high risk of progression in SMM. Madan and colleagues studied 175 patients with SMM to determine the predictive value of PC proliferative rate measured using a slide-based immunofluorescence method, the PC labeling index (PCLI).[36] The median TTP was 1.2 years in patients with a PCLI value ≥1 vs 2.6 years in those with a PCLI value <1 ($P < .001$). The PCLI is limited by lack of availability in the clinical setting. We are awaiting data from proliferative rates assessed using flow cytometric methods.

Risk stratification of SMM

Two models that have been well studied and subsequently validated in a prospective trial include the one proposed by the Mayo Clinic group and another proposed by the Spanish Myeloma Group.[1,21] The Mayo Clinic model uses the size of the serum M protein and the extent of bone marrow involvement. These 2 variables are used to classify SMM into 3 risk groups: group 1 with serum M protein ≥3g/dL and ≥10% BMPCs, group 2 with <3 g/dL M protein and ≥10% BMPCs, and group 3 with M protein ≥3 g/dL but BMPCs <10%. The median TTP to symptomatic MM is significantly different among the 3 groups: 2, 8, and 19 years, respectively. The probability of progression at 15 years is 87%, 70%, and 39%, respectively. The model developed by the Spanish Myeloma Group uses the presence of 2 risk factors in patients with SMM who have ≥10% BMPCs: presence of an aberrant PC immunophenotype in >95% of clonal PCs and immunoparesis (reduction in ≥1 uninvolved immunoglobulins by >25% compared to normal).[21] Patients with both risk factors have a median TTP of 23 months compared to 73 months when only 1 risk factor is present (either aberrant PCs or immunoparesis) and not reached when neither risk factor is present. In a recent randomized trial, patients were considered high risk if they met either the Mayo Clinic or the Spanish Myeloma Group criteria for high risk SMM.[5] The trial showed that patients meeting these criteria had a median TTP of 24 months without therapy, confirming the validity of these criteria.

The Mayo Clinic and Spanish models enable initial risk stratification of SMM that can then be refined using additional prognostic factors. For example, Dispenzieri and colleagues have shown that the prognostic value of the initial Mayo Clinic model can be improved by adding the serum FLC ratio as a variable.[26] Each model appears to identify unique patients as high risk, with some, but not complete, overlap.[37] We believe that the classification of high-risk SMM is critical and should be based on all available data on a given patient rather than a restricted set of variables. Revised criteria for high-risk SMM that incorporate the Mayo Clinic and Spanish Myeloma Group criteria, as well as other risk factors that have been well studied and that identify patients with a similar risk of progression (~50% risk of progression within 2 years) are listed in Table 2. Patients defined as having high-risk SMM using these criteria need close follow-up and are candidates for clinical trials investigating the value of early therapy.

Diagnostic evaluation

Baseline studies should include complete blood count, serum creatinine, serum calcium, skeletal survey, serum protein electrophoresis with immunofixation, 24-hour urine protein electrophoresis with immunofixation, and serum FLC assay.[38] Specialized imaging with at least one method such as MRI of the spine and pelvis (ideally whole-body MRI) or ^{18}F-fluorodeoxyglucose PET-CT or low-dose whole body CT is recommended to exclude MM.[7,38,39] Bone marrow examination is required, and should include fluorescent in situ hybridization studies to detect high-risk cytogenetic abnormalities as well as PC immunophenotyping by multiparametric flow cytometry to enable accurate risk stratification (Table 2).

The M protein, serum FLC levels, complete blood count, calcium, and creatinine should be re-evaluated every 3 to 4 months. In high-risk patients, follow-up should continue indefinitely and include periodic imaging studies to rule out asymptomatic progression. In low-risk patients, follow-up can be reduced to once every 6 months after the first 5 years. In both groups, development of symptoms suggestive of MM or related disorders should be carefully pursued.

In patients with baseline abnormalities on MRI scans, an increase in number and/or size of focal lesions during follow-up has diagnostic and prognostic value.[40] Therefore, in patients with MRI scans showing diffuse infiltration, solitary focal lesion, or equivocal lesions, follow-up examinations in 3 to 6 months are strongly recommended.[7]

Treatment

The standard of care for SMM has been observation.[3,41,42] However, it is well recognized that the term SMM encompasses patients with early malignancy (MM) that is still asymptomatic, patients with premalignancy who are at high risk of progression, as well as patients with premalignancy for whom the progression rate is more in line with MGUS rather than that reported for SMM.[1,43] The International Myeloma Working Group (IMWG) has revised the diagnostic criteria for MM, and a subset of patients with early malignancy is now

considered MM and treated as such.[7] But clearly not all patients with early malignancy can be captured by the new IMWG criteria. SMM still includes a high-risk subgroup (Table 2) with an ~50% risk of progression within 2 years, and these patients need to be considered for clinical trials testing early therapy.[20]

The rationale for observation as the standard of care for SMM over the years has been the lack of clear data from randomized trials of an overall survival or quality-of-life benefit with early therapy, the toxicity of therapy in an asymptomatic patient population, and the fact that some patients can be free of progression for many years without any therapy.[6] There is also a concern that early therapy may increase the risk of selecting resistant clones. We therefore need to accurately identify patients who are most likely to benefit from intervention. Although, there are still no laboratory methods to definitively differentiate clonal premalignancy (biological MGUS) from clonal malignancy (biological MM), we now have several biomarkers that help us identify the patients with SMM who are at the greatest risk of progression.[44]

Early studies

Three small studies compared early therapy with melphalan plus prednisone vs observation or melphalan plus prednisone treatment at the time of progression.[45-47] These studies found no significant improvement in overall survival with early therapy.

Bisphosphonates

In a small trial, no significant antitumor effect was seen with pamidronate.[48] In a subsequent randomized trial, pamidronate administration (60-90 mg once a month for 12 months) was compared to observation in 177 patients with SMM.[49] There was no improvement in TTP or overall survival with pamidronate. However, a reduction in skeletal-related events (SREs) was noted with pamidronate compared to observation (SRE rate at progression, 39% vs 73%, respectively; $P = .009$). In another randomized trial, 163 patients with SMM were randomized to zoledronic acid (4 mg once a month for 12 months) vs observation.[50] There was no significant difference in TTP (median TTP, 67 months vs 59 months with zoledronic acid and observation, respectively; $P = .8312$). However, as with pamidronate, a reduction in the rate of SREs was noted (56% vs 78%, respectively; $P = .041$).

Thalidomide

Two small phase 2 trials initially evaluated the role of thalidomide in patients with SMM.[51,52] However, therapy was limited by the development of neuropathy in most patients. In a subsequent phase 2 trial of 76 eligible patients with SMM, thalidomide was combined with pamidronate.[53] However, a reduction in dose of thalidomide due to adverse events was needed in 86% of patients within the first 2 years.

In a randomized trial, Witzig and colleagues compared thalidomide plus zoledronic acid vs zoledronic acid alone in 68 patients with SMM.[54] TTP was superior with thalidomide plus zoledronic acid vs zoledronic acid alone (median TTP, 2.4 vs 1.2 years, respectively; $P = .02$). Partial response or better was seen in 37% vs 0%, respectively ($P < .001$). However, there were no significant differences in TTP to symptomatic MM (4.3 vs 3.3 years, respectively) or overall survival (5-year survival, 74% vs 73%, respectively).

Lenalidomide

In a recent randomized trial, the Spanish Myeloma Group tested the combination of lenalidomide and low-dose dexamethasone (Rd) vs observation in 120 patients with high-risk SMM.[5] TTP was significantly longer in patients treated with Rd as compared with the observation group (median TTP, not reached vs 21 months, $P < .001$). Ninety percent of patients treated with Rd achieved a partial response, including 26% who achieved a complete response (CR). Symptomatic disease developed in 13 patients (23%) assigned to Rd vs 47 patients (76%) assigned to observation. Overall survival was longer with Rd compared to observation (3-year survival rate, 94% vs 80%, respectively; $P = .03$). This study shows for the first time that the overall survival of high-risk SMM patients can be improved by effective early treatment.

Although the Spanish study results are of importance, there are some limitations that affect generalizability. For example, a high proportion of patients who progressed from SMM to MM within the first 6 months were diagnosed as having MM due to lytic bone lesions, and it is possible that with routine MRI or PET-CT studies, these patients can be identified at baseline. Second, we also need to determine whether patients, identified as high risk using the criteria listed in Table 2 (ie, criteria other than those used in the Spanish trial), would benefit in a similar manner from therapy. Third, some have argued that waiting for end-organ damage in the control arm rather than initiating therapy at the time of biological progression (as was done in the treatment arm with the addition of dexamethasone) may have biased the trial in favor of early therapy.[55] Although this criticism could be the subject of a subsequent phase 3 trial, at the time the Spanish trial was conducted, the standard of care in the control arm was indeed observation until end-organ damage occurs. The trial thus showed that such an approach is not optimal for high-risk patients and provided the impetus for eliminating the reliance on CRAB features as a requirement to start therapy.[7] Lastly, the trial was not designed for regulatory purposes and, therefore, results need to be reproduced by other studies. In line with this, a randomized trial being conducted by the Eastern Cooperative Oncology Group comparing lenalidomide to observation will be of value.

Combination therapy

Some patients with high-risk SMM are interested in more aggressive treatment options targeting stringent CR, minimal residual disease (MRD)-negative state, and possible cure. Zingone and colleagues have recently reported on 12 patients with high-risk SMM in a phase 2 trial using carfilzomib (a second-generation proteasome inhibitor), lenalidomide, and dexamethasone.[56] In an interim analysis, 7 of 12 patients (58%) achieved CR or stringent CR. Among these 7 patients, 6 were MRD negative on a sensitive multiparametric flow cytometry assay. Additional patients are being enrolled, and further results are awaited.

Recommendations for therapy

The standard of care for SMM remains observation until development of symptomatic MM.[3,38,41,42] The updated IMWG diagnostic criteria for MM allows us now to initiate therapy before end-organ damage on the basis of specific biomarkers, and also allows the use of sensitive imaging criteria to diagnose MM, including PET-CT and MRI.[7] Thus, patients with high-risk SMM who are being observed can be initiated on therapy without waiting for CRAB features to appear.

We recommend that patients with high-risk SMM (Table 2) be offered clinical trials testing early intervention. These patients need close follow-up indefinitely, as discussed earlier.[44] Selected high-risk SMM patients with multiple risk factors or evidence of biological progression (rising M protein level) can be considered for therapy. There are no specific factors to make this determination, and clinical

judgment is needed. If therapy is chosen, peripheral blood stem cells should be collected for cryopreservation after ~4 cycles of therapy.[57,58] Patients treated with Rd also need appropriate thromboprophylaxis.[58,59] When possible, it is important for these patients to be referred to centers specializing in MM therapy. Patients with low-risk SMM who are stable and free of progression after 5 years can be followed less often.

Bisphosphonates (pamidronate or zoledronic acid) administered using the MM dosing schedule (once a month) are not recommended for patients with SMM. Once-yearly bisphosphonate used for the treatment of osteoporosis is appropriate. More frequent dosing every 3 to 4 months can be considered for selected high-risk SMM patients.

Future directions

SMM is an excellent setting to test the impact of several new treatment options in development, including the oral proteasome inhibitor ixazomib,[60,61] elotuzumab,[62] daratumumab,[63] and pomalidomide.[64] Studies using both molecular-based (eg, VDJ sequencing) and multiparametric flow cytometry–based MRD detection are needed to compare sensitivity, feasibility, and other important aspects.

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